WE CLAIM:

1. An antigen-binding protein comprising a complex of two first polypeptides and two second polypeptides,

said first polypeptide having an antigen-binding site located to the N terminus of an immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with an immunoglobulin heavy chain first constant domain (C_H1 domain), and

said second polypeptide having an antigen-binding site located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association.

2. The antigen-binding protein of Claim 1 wherein one or more of said antigen-binding sites are provided by a single chain Fv.

3. The antigen-binding protein of Claim 1 wherein said antigen-binding sites of said first and second polypeptides have different specificities.

4. The antigen-binding protein of Claim 1 wherein said antigen-binding sites of said first and second polypeptides have the same specificity.

5. The antigen-binding protein of Claim 3 wherein said specificities are for epitopes which reside on different antigens.

6. The antigen-binding protein of Claim 3 wherein said specificities are for epitopes which reside on the same antigen.

7. The antigen-binding protein of Claim 1 wherein said first polypeptide and said second polypeptide are covalently bound together.

8. The antigen-binding protein of Claim 1 wherein said two second polypeptides are covalently bound together.

9. The antigen-binding protein of Claim 1 wherein said second polypeptide has C_H1, C_H2 and C_H3 domains of an antibody of isotype IgA, IgD or IgG.

10. The antigen-binding protein of Claim 1 wherein said second polypeptide has C_H1, C_H2, C_H3 and C_H4 domains of an antibody of isotype IgE or IgM.

11. The antigen-binding protein of Claim 1 wherein said constant domains are mammalian constant domains.

12. The antigen-binding protein of Claim 1 wherein said constant domains are human constant domains.

13. The antigen-binding protein of Claim 1 wherein one or more of said single chain Fvs are mouse single chain Fvs.

14. The antigen-binding protein of Claim 1 wherein one or more of said single chain Fvs are chimeric single chain Fvs having human framework regions.

15. The antigen-binding protein of Claim 1 wherein said single chain Fv has human V_L and V_H domains.

16. The antigen-binding protein of Claim 1 wherein the heavy chain constant domains capable of stable self association are selected from the group consisting of C_H2, C_H3, and C_H4 domains from any immunoglobulin isotype or subtype.

17. The antigen-binding protein of Claim 1 which is capable of binding to an Fc receptor.

18. The antigen-binding protein of Claim 1 which is capable of effecting complement mediated cytotoxicity (CMC).

19. The antigen-binding protein of Claim 1 which is capable of effecting antibody dependent cell-mediated cytotoxicity (ADCC).

20. The antigen-binding protein of Claim 1 which is linked to an anti-tumor agent.

21. The antigen-binding protein of Claim 1 which is linked to a detectable signal producing agent.

22. The antigen-binding protein of Claim 1 which neutralizes activation of a VEGF receptor.

23. The antigen-binding protein of Claim 22 wherein the VEGF receptor is mammalian.

24. The antigen-binding protein of Claim 22 wherein the VEGF receptor is human.

25. The antigen-binding protein of Claim 24 wherein the VEGF receptor is encoded by the flt-1 or flk-1 gene.

26. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for KDR.

27. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for FLT1.

28. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for FLT4.

29. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for EGF-R.

30. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for HER2.

31. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for FGF-R.

32. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for PDGF-R.

33. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for a receptor tyrosine kinase.

34. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for Tek.

35. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for Tie-2.

36. The antigen-binding protein of Claim 1 wherein one of the antigen-binding sites is specific for KDR and the other antigen-binding site is specific for FLT1.

37. The antigen-binding protein of Claim 1 wherein one of the antigen-binding sites is specific for KDR and the other antigen-binding site is specific for an antigen selected from the group consisting of FLT4, EGF-R, HER2, FGF-R, PDGF-R, Tek and Tie2.

38. The antigen-binding protein of Claim 1 wherein one of the antigen-binding sites is specific for EGF-R and the other antigen-binding site is specific for HER2.

39. The antigen-binding protein of Claim 1 wherein at least one of the antigen-binding sites is specific for a cell-surface antigen of an immune system effector cell.

40. The antigen-binding protein of Claim 39 wherein the immune system effector cell is a T cell, a macrophage, a neutrophil, or an NK cell.

41. The antigen-binding protein of Claim 39 wherein the cell-surface antigen is CD3, CD16, CD28, CD32, CD64, an Fc receptor, a cytokine receptor or a lymphokine receptor.

42. The antigen-binding protein of Claim 39 wherein the cell-surface antigen is a receptor for a cytokine or lymphokine and wherein an antigen-binding site comprises the amino acid sequence of the cytokine or lymphokine or a portion thereof.

43. The antigen-binding protein of Claim 42 wherein the receptor is for IL-2, IL-4, IL-5, GM-CSF or G-CSF.

44. The antigen-binding protein of any one of Claims 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35 wherein one of the one of the antigen-binding sites is specific for a cell-surface antigen of an immune system effector cell.

45. The antigen-binding protein of Claim 44 wherein the immune system effector cell is a T cell, a macrophage, a neutrophil, of an NK cell.

46. The antigen-binding protein of Claim 44 wherein the cell-surface antigen is CD3, CD16, CD28, CD32, CD64, an Fc receptor, a cytokine receptor or a lymphokine receptor.

47. An antigen-binding protein comprising a complex of two first polypeptides and two second polypeptides,

said first polypeptide having a single chain Fv located to the N terminus of an immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with an immunoglobulin heavy chain first constant domain (C_H1 domain), and

said second polypeptide having a single chain Fv located to the N terminus of said C_H1 domain, said C_H1 domain followed by one or more heavy chain constant domains capable of stable self-association.

48. The antigen-binding protein of Claim 47 wherein said antigen-binding sites of said first and second polypeptides have different specificities.

49. The antigen-binding protein of Claim 47 wherein said antigen-binding sites of said first and second polypeptides have the same specificity.

50. The antigen-binding protein of Claim 47 which neutralizes activation of KDR.

51. The antigen-binding protein of Claim 50 wherein one or both of said single chain Fvs is single chain Fv p1c11.

52. The antigen-binding protein of Claim 50 wherein one or both of said single chain Fvs is single chain Fv p4G7.

53. The antigen-binding protein of Claim 47 which neutralizes activation of FLT1.

54. The antigen-binding protein of Claim 53 wherein one or both of said single chain Fvs is single chain Fv 6.12.

55. The antigen-binding protein of Claim 50 wherein the amino acid sequence of the complementarity determining regions (CDRs) of one or both of said single chain Fv is represented by:

SEQ ID NO: 1 at CDRH1;
SEQ ID NO: 2 at CDRH2;
SEQ ID NO: 3 at CDRH3;
SEQ ID NO: 4 at CDRL1;
SEQ ID NO: 5 at CDRL2; and
SEQ ID NO: 6 at CDRL3.

56. The antigen-binding protein of Claim 50 wherein the nucleotide sequence encoding the complementarity determining regions (CDRs) of one or both of said single chain Fv is represented by:

SEQ ID NO: 9 for CDRH1;

SEQ ID NO: 10 for CDRH2;

SEQ ID NO: 11 for CDRH3;

SEQ ID NO: 12 for CDRL1;

SEQ ID NO: 13 for CDRL2; and

SEQ ID NO: 14 for CDRL3.

57. The antigen-binding protein of Claim 50 wherein the amino acid sequence of the variable domains of one or both of said single chain Fv is represented by:

SEQ ID NO: 7 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 8 for the light-chain variable domain (V_L).

58. The antigen-binding protein of Claim 50 wherein the nucleotide sequence encoding the variable domains of one or both of said single chain Fv is represented by:

SEQ ID NO: 15 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 16 for the light-chain variable domain (V_L).

59. The antigen-binding protein of Claim 50 wherein the amino acid sequence of the complementarity determining regions (CDRs) of one or both of said single chain Fv is represented by:

SEQ ID NO: 1 at CDRH1;

SEQ ID NO: 21 at CDRH2;

SEQ ID NO: 3 at CDRH3;

SEQ ID NO: 4 at CDRL1;

SEQ ID NO: 5 at CDRL2; and

SEQ ID NO: 6 at CDRL3.

60. The antigen-binding protein of Claim 50 wherein the nucleotide sequence encoding the complementarity determining regions (CDRs) of one or both of said single chain Fv is represented by:

SEQ ID NO: 9 for CDRH1;

SEQ ID NO: 24 for CDRH2;

SEQ ID NO: 11 for CDRH3;

SEQ ID NO: 12 for CDRL1;

SEQ ID NO: 13 for CDRL2; and

SEQ ID NO: 14 for CDRL3.

61. The antigen-binding protein of Claim 50 wherein the amino acid sequence of the variable domains of one or both of said single chain Fv is represented by:

SEQ ID NO: 22 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 23 for the light-chain variable domain (V_L).

62. The antigen-binding protein of Claim 50 wherein the nucleotide sequence encoding the variable domains of one or both of said single chain Fv is represented by:

SEQ ID NO: 25 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 26 for the light-chain variable domain (V_L).

63. The antigen-binding protein of Claim 50 wherein one or both of said single chain Fv has a nucleotide sequence represented by SEQ ID NO: 27 or SEQ ID NO: 28.

64. A method for making an antigen-binding protein, which comprises

(a) coexpressing in a host cell

a recombinant DNA construct encoding a first polypeptide having an antigen-binding site located to the N terminus of an immunoglobulin light chain constant domain (C_L domain), said C_L domain capable of stable association with an immunoglobulin heavy chain first constant domain (C_H1 domain), and

a recombinant DNA construct encoding a second polypeptide having an antigen-binding site located to the N terminus of said C_H1 domain, said C_H1 domain

followed by one or more heavy chain constant domains capable of stable self-association,

for a time and in a manner sufficient to allow expression of said polypeptides and formation of said antigen binding protein; and

(b) recovering said antigen binding protein.

65. The method of Claim 64 wherein said constructs are on the same DNA expression vector.

66. The method of Claim 64 wherein said constructs are on different DNA expression vectors.

67. The method of Claim 64 wherein said host cell is a bacterial cell, a yeast cell or a mammalian cell.

68. The method of Claim 64 wherein said antigen-binding protein is secreted from the host cell.

69. A method of neutralizing the activation of a VEGF receptor, which comprises treating a cell with an antigen-binding protein of Claim 1 in an amount sufficient to neutralize activation of said receptor.

70. The method of Claim 69 wherein at least one of the antigen-binding sites is specific for KDR.

71. The method of Claim 69 wherein at least one of the antigen-binding sites is specific for FLT1.

72. A method of reducing tumor growth which comprises treating a cell with an antigen-binding protein of Claim 1, wherein at least one of the antigen binding sites is specific for a VEGF receptor, in an amount sufficient to reduce tumor growth.

73. The method of Claim 72 wherein at least one of the antigen-binding sites is specific for KDR.

74. The method of Claim 72 wherein at least one of the antigen-binding sites is specific for FLT1.

75. A method of inhibiting angiogenesis which comprises treating a cell with an antigen-binding protein of Claim 1, wherein at least one of the antigen binding sites is specific for a VEGF receptor, in an amount sufficient to inhibit angiogenesis.

76. The method of Claim 75 wherein at least one of the antigen-binding sites is specific for KDR.

77. The method of Claim 75 wherein at least one of the antigen-binding sites is specific for FLT1.